American Journal of Medical Genetics 62:336–338 (1996)

Familial Congenital Bicuspid Aortic Valve: A Disorder of Uncertain Inheritance

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Congenital bicuspid aortic valve (BAV) is one of the most frequent heart defects detected by echocardiographic investigation and necropsy (0.9–1% of the general population), but only 16 families with familial congenital BAV have been described up to now. We report on a family in which 4 members of two generations (2 brothers, 1 sister, and her son) are affected with BAV. The BAV mode of inheritance is discussed. © 1996 Wiley-Liss, Inc.

KEY WORDS: bicuspid valve, congenital malformation, genetic counseling

INTRODUCTION

Bicuspid aortic valve (BAV) is one of the commonest forms of congenital heart defect observed in adults, with an estimated prevalence in the general population of 0.9–1% [Michels and Riccardi, 1990]. BAV may be part of several malformation syndromes, may be associated with other cardiac malformations, particularly coarctation of the aorta [Kappetein et al., 1991], or, more frequently, may present as an isolated congenital anomaly.

The cause of isolated BAV is at present unknown. Most cases are sporadic, and only few familial cases have been described. In fact, following the report by McKusick [1972] of BAV in a father and his 17-year-old son, on the whole only 16 families with familial congenital BAV have been described [Gale et al., 1977; Emanuel et al., 1978; Godden et al., 1987; McDonald and Maurer, 1989; Glick and Roberts, 1994]. The mode of inheritance is not defined; however, there is some evidence [on-line McKusick No. 109730] that BAV is inherited as an autosomal-dominant trait, with incomplete penetrance particularly in females. In this report we present a new family in which 4 members in two generations are affected with BAV, and we discuss the mode of inheritance.

Received for publication September 21, 1994; revision received December 23, 1994.

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CLINICAL REPORTS

The pedigree is shown in Figure 1.

Patient 1 (III-6)

The propositus, age 11 years, was referred because of a heart defect. He was the second child of unrelated parents and was born through cesarean section at 40 gestational weeks after an uneventful pregnancy. Birth weight was 3,150 g (25th centile), length was 49 cm (10th–25th centile), and the neonatal period was normal. Neurological and physical development was normal.

In the first years of life no significant disease was reported, except for recurrent ear infection. At age 5 years, during a hospital admission because of high fever, the child was found to have a murmur that was investigated through echocardiography, in view of the family history of BAV. The echocardiography showed a bicuspid aortic valve without aortic stenosis or incompetence; the other cardiac structures appeared normal. The results of routine laboratory investigations and the electrocardiogram were normal. Since then, echocardiographic investigations have been performed yearly; the most recent (at age 11 years) showed an aortic kinking with a maximal systolic gradient of 15 mm Hg (consistent with a normal valvular function), a mild aortic regurgitation, and mitral and tricuspid valve prolapse without a significant incompetence of the valve. Furthermore, a mild dilatation of the ascending aorta was noted.

Phenotype analysis at age 11 years did not show craniofacial or other physical anomalies; weight was 33 kg (50th centile), height was 142.5 cm (50th centile), and occipitofrontal circumference was 53 cm (−0.1 SD). A mild pectus carinatum (chest circumference, 66.5 cm, 25th centile; intermamillary distance, 14.5 cm, 10th centile) was present. There was a precordial lift with a 2/6 systolic murmur.

Patient 2 (II-3)

L.V., the 47-year-old mother of patient 1, underwent a cardiac evaluation because of the occurrence of arrhythmia, after the diagnosis of BAV in her son. She had no history of hypertension, hyperlipidemia, or rheumatic fever; her two pregnancies had taken a regular course. At present she works as a school caretaker.

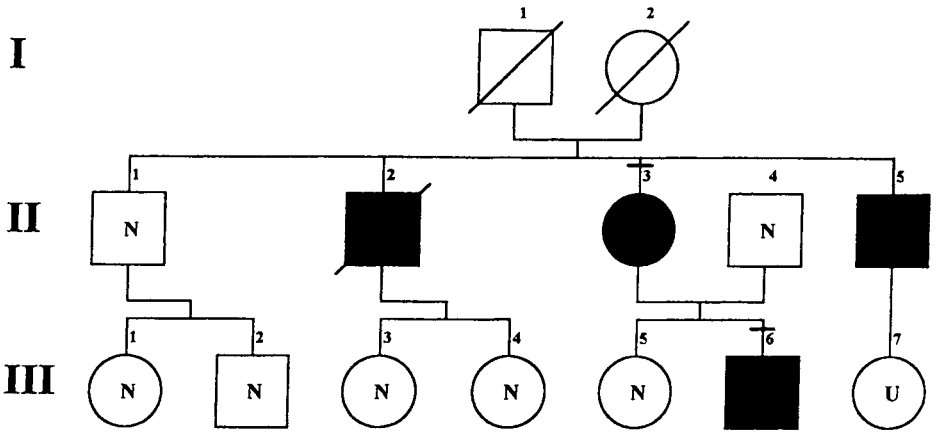

Fig. 1. Pedigree of the family. N, normal at investigation; U, not investigated. Members I1 and I2 were dead (heart disease?) before investigation.

Physical examination was normal, except for a precordial systolic murmur and an irregular heart rhythm. There were no signs of heart failure, and blood pressure was within normal range.

The results of routine hematological investigations were all normal. Electrocardiogram showed an atrioventricular block, and echocardiography demonstrated a BAV with mild incompetence; cardiac volumes, parietal width, and kinesis appeared normal. The patient therefore underwent periodic cardiological follow-up. No physical anomalies or malformations were present.

Patient 3 (II-2)

Pregnancy, delivery, and childhood of L.G. were reportedly normal. He was declared fit for military service, had 2 daughters, and was well until age 40, when he was found to have a cardiac murmur. Echocardiography demonstrated BAV with severe aortic stenosis. At that time the patient was asymptomatic and refused further clinical investigations.

Seven years later the patient was admitted to hospital for abdominal pain. A cardiac ultrasound examination showed a worsening of the previous findings: the BAV appeared heavily calcified and severely stenotic, and mitralic regurgitation was also noted.

Electrocardiogram showed a left bundle branch block. Blood pressure and heart rate were normal. Routine laboratory tests were normal, as well as abdominal ultrasound and thoracic roentgenograms.

After 1 month the patient presented a severe pulmonary edema followed by cardiogenic shock that caused his death a few hours later. Necropsy was not performed.

Patient 4 (II-5)

L.M., the 42-year-old brother of patient 3, was found to have a murmur and was studied after the death of patient 3. The patient has been completely asymptomatic. Ultrasound examination showed BAV with severe regurgitation and dilatation of the left ventricle associated with mild mitral regurgitation. At present the patient is asymptomatic. He is scheduled for valvuloplastic surgery.

Family Screening

The grandparents (Fig. 1; I-1, I-2) were dead of unspecified heart disease before the identification of BAV in their children. No examinations or autopsies were performed. All relatives, except for the 18-month-old daughter of II-5 who was normal at physical examination, were investigated by echocardiography and were normal.

DISCUSSION

We report on a family in which 4 members of both sexes in two generations are affected with BAV. No information is available about the first-generation members, dead because of an unspecified cardiopathy. This observation is rare; in fact, although isolated BAV is the most common congenital malformation of cardiac valves, its familial occurrence is extremely uncommon. Up to now, familial cases have been described only 16 times [McKusick, 1972; Gale et al., 1977; Emanuel et al., 1978; Godden et al., 1987; McDonald and Maurer, 1989; Glick and Roberts, 1994]. This lack of observation may be due to diagnostic difficulties, at least in the past when the diagnosis was made on the basis of clinical observation, insufficient for BAV identification [Pachulsky and Chan, 1993]. For example, the only clinical finding in our patients 1, 2, and 4 was a murmur, and the diagnosis of BAV was made only by ultrasound.

For the same reason, no epidemiological studies are available at present, and only one clinicogenetic study of 41 families has been performed [Emanuel et al., 1978] following the first report of a familial case by McKusick [1972].

The mode of inheritance of BAV is still uncertain; Emanuel et al. [1978] concluded that it is most probably multifactorial, except for some rare autosomal-dominant cases. Kappetein et al. [1991] hypothesized that BAV as left-sided obstructive lesions, such as coarctation of the aorta, may be due to a genetic-environmental disorder of the neural crest. On the basis

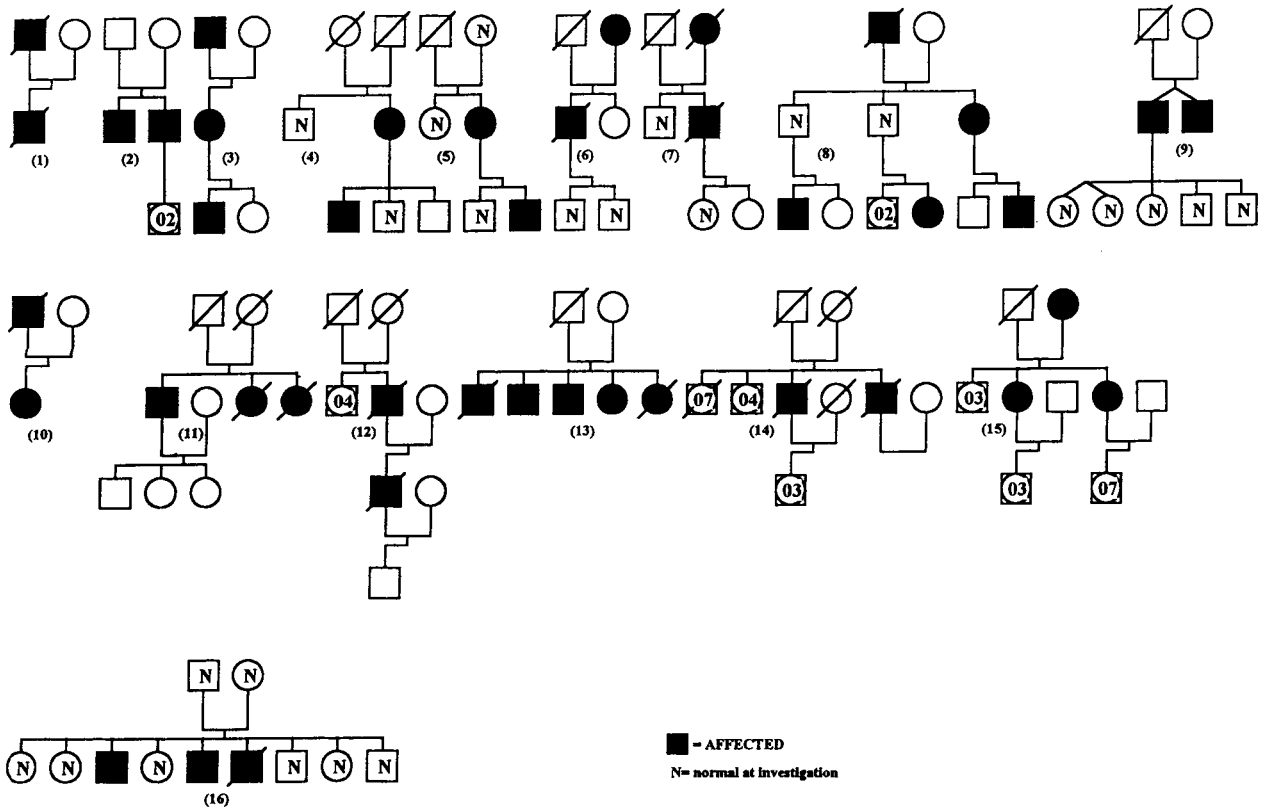

Fig. 2. Pedigrees of the 16 published BAV families. References: 1, McKusick [1972]; 2, Gale et al. [1977]; 3–8, Emanuel et al. [1978]; 9, Godden et al. [1987]; 10–15, Glick and Roberts [1994]; 16, McDonald and Maurer [1989].

of the published data, BAV has been included among the autosomal-dominant phenotypes [on-line McKusick No. 109730] with reduced penetrance mainly in females.

However, analysis of the published pedigrees (Fig. 2), and of our own, shows that 9 of 17 families with familial BAV have affected members in two generations; only two families show a three-generation transmission (Fig. 2, families 3 and 8); five families have only affected sibs and parents not available for investigation; and in only one family (Fig. 2, family 16), 3 brothers were affected and the parents were normal.

This extremely low proportion of affected relatives does not fit with the above-mentioned hypotheses of multifactorial etiology and autosomal-dominant mutations. In fact, isolated BAV is so frequent that if it were not genetically determined, only by chance at least 1% of relatives of affected subject should be also affected. This lack of reported familial cases may be due to one or both of the following causes: 1) underestimation of recurrence in relatives because of a lack of information (autopsy) or investigation (echocardiography) in most instances; or 2) heterogeneity with most cases nongenetic, while a few cases are inherited as autosomal-dominant.

Complex segregation analysis, using data of epidemiological and genetic studies, should be performed to test the genetic hypothesis and to define the BAV mode of inheritance.

In conclusion, we reconfirm the importance of echocardiographic investigation in all first-degree relatives of patients affected with BAV, in order to give appropriate genetic counseling. At present, in absence of a definite mode of inheritance, a recurrence risk as high as 50% at least for familial cases should be provided.

REFERENCES

Emanuel R, Withers R, O'Brien K, Ross P, Feizi O (1978): Congenitally bicuspid aortic valve. Clinicogenetic study of 41 families. Br Heart J 40:1402–1407.

Gale AN, McKusick VA, Hutchins GH, Gott VL (1977): Familial congenital bicuspid aortic valve. Chest 72:668–670.

Glick BN, Roberts WC (1994): Congenitally bicuspid aortic valve in multiple family members. Am J Cardiol 73:400–404.

Godden DJ, Sandhu PS, Kerr F (1987): Stenosed bicuspid aortic valves in twins. Eur Heart J 8:316–318.

Kappetein AP, Gittemberger-de Groot AC, Zwinderman AH, Rohmer J, Poelmann RE, Huysmans HA (1991): The neural crest as a possible pathogenetic factor in coarctation of aorta and bicuspid aortic valve. J Thorac Cardiovasc Surg 102:830–832.

McDonald K, Maurer BJ (1989): Familial aortic valve disease: Evidence for a genetic influence? Eur Heart J 10:676–677.

McKusick V (1972): Association of congenital bicuspid aortic valve and Erdheim's cystic medial necrosis. Lancet 1:1026–1027.

Michels VV, Riccardi VM: Congenital heart defects. In Emery AHE, Rimoin DL (eds): "Principles and Practice of Medical Genetics," Churchhill, Livingstone, London: pp 1223–1224.

Pachulsky RT, Chan K-L (1993): Progression of aortic valve dysfunction in 51 adult patients with congenital bicuspid aortic valve: Assessment and follow-up by Doppler echocardiography. Br Heart J 69:273–240.